Decrease of muscle volume in chronic kidney disease: the role of mitochondria in skeletal muscle.

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ABSTRACT

Reduced muscle volume and impaired exercise endurance are well-documented phenomena in chronic kidney disease and the relevant molecular mechanisms have been gradually unveiled. Tamaki *et al.* demonstrate the novel mechanism of reduced exercise endurance in renal insufficiency, which is due to the reduction of mitochondria content in skeletal muscles. In addition, they show that a high protein diet reduces exercise endurance through an inhibition of muscle pyruvate dehydrogenase. This study clarifies a novel mechanism of reduced muscle volume and impaired exercise endurance in patients with renal insufficiency.

Physical activity plays a major role in patient mortality and morbidity; however, exercise performance and endurance is known to decline in patients with chronic kidney disease (CKD)[1]. These individuals are at a higher risk for cardiovascular diseases because of this reduced exercise performance and endurance. Previous studies have shown that increased levels of inflammatory cytokines are associated with decreased mobility and subsequent development of disabilities due to a deterioration of muscle strength. To date, efforts have been made to reveal the molecular mechanisms involved in the association between decreased muscle volume and CKD. Muscle mass reduction is considered to be due to, at least in part, an imbalance in protein synthesis and degradation via the ubiquitin-proteasome system,[2] acid–base imbalance,[3] insulin resistance,[3] inflammation, and decreased exercise ability. The insulin-like growth factor I (IGF-1)/insulin receptor substrate 1 (IRS-1)/phosphatidylinositol 3-kinase (PI3K)/Akt pathway is considered to be a key pathway in protein degradation.[2,3] Activation of the PI3K/Akt pathway supports multiple mechanisms for cellular proliferation, apoptosis inhibition, cellular migration, and cytoskeletal organization. The Akt protein family of serine/threonine kinases is central to the regulation of and adaptation to many cellular stress-induced processes. Decreased Akt phosphorylation activates the ubiquitin pathway, which promotes muscle volume reduction through caspase-3 activation. In CKD, the E3 ubiquitin-conjugating enzyme is activated to promote protein degradation. Two ubiquitin ligases, atrogin-1/muscle atrophin F-box (MAFbx) and muscle ring finger 1 (MuRF1), are specifically expressed in muscle tissues and are

known to correlate with muscle atrophy. Furthermore, caspase-3 activation gives rise to expression of a 14-kDa actin fragment, a potential marker of muscle mass reduction (Figure 1).

Mitochondria are highly differentiated subcellular organelles that produce ATP via oxidative phosphorylation.[4] They are essential organelles that maintain the muscle mobility necessary for physical activity. Exercise endurance is closely associated with mitochondria concentrations in muscle tissues and electron transport complex activity. ATP is also produced by glycolysis and the tricarboxylic acid (TCA) cycle. Pyruvate dehydrogenase regulates the entry of glycolytic products into the TCA cycle via oxidative decarboxylation of pyruvate to acetyl-CoA in the mitochondria of mammalian cells. Several studies have reported a decrease in pyruvate dehydrogenase activity in rat muscles in response to fasting and in diabetic models.[5] In contrast, exercise- or contraction-induced increases in pyruvate dehydrogenase activity have been demonstrated in both human and rat models.[5] Pyruvate dehydrogenase is considered to be a key enzyme responsible for switching from anaerobic to aerobic carbohydrate metabolism.

AMP-activated protein kinase (AMPK) is a key regulator that inactivates acetyl CoA carboxylase, thereby promoting fatty acid oxidation and mitochondrial biogenesis.[6] Administration of 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), an AMPK activator, to rats results in increased skeletal muscle citrate synthase and cytochrome C activity, suggesting an increased amount of mitochondria. One of the mechanisms by which AMPK regulates the expression of mitochondrial

enzymes involves regulating various transcription factors, including peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which is considered to be the vital regulator of mitochondrial content in mammalian tissues (Figure 1). PGC-1α was originally shown to induce mitochondrial biogenesis in cultured myocytes. Furthermore, PGC-1α overexpression in skeletal muscles increases type 1 fiber activity and subsequent resistance to muscle fatigue.

In addition to the above-mentioned molecular mechanisms, Tamaki *et al.*[7] clarified the new mechanism in the reduction of exercise endurance and muscle volume in mice with renal insufficiency by focusing on the decrease of muscle mitochondria. Although the C57BL/6 strain is well known to be resistant against renal insufficiency after 5/6 nephrectomy,[8] the authors successfully developed mice with renal insufficiency in this study. They investigated age differences in muscle volume, and found that young mice with 5/6 nephrectomy showed a decrease in mitochondria content in type I (slow oxidative) and IIa (fast oxidative glycolytic) skeletal muscles and running distance, despite the preservation of muscle volume and strength. Type I fibers are characterized by increased mitochondria content and oxidative state. Young mice also showed an increase in 14-kDa actin fragment content and caspase-3 expression, indicating increased protein degradation in skeletal muscle. Furthermore, a reduction of PGC-1α and phosphorylated AMPK were also found in these mice, indicating decreased mitochondria content. In contrast, aged mice lost muscle volume and power, in addition to the reduction in skeletal muscle mitochondria content. The underlying mechanism by which aged mice

lost muscle volume might be dependent on prolonged activation of the proteasome pathway. The authors further demonstrated that a high protein diet increased muscle mass and strength but reduced muscle endurance as characterized by reduced mitochondria content and AMPK activation. A high protein diet elicits the accumulation of lactate and the reduction of pyruvate dehydrogenase, leading to physical performance impairment that is probably due to oxidative stress. The previous report also showed the deteriorative effect of a high protein diet in renal failure on body physique: rats with chronic renal failure fed a high protein diet exhibited reduced body weight and length compared with those fed a normal protein diet because of anorexia, uremia, and acidosis.[9] Lastly, they successfully demonstrated that the pyruvate dehydrogenase activator, dichloroacetate (DCA), could recover running distance, supporting their hypothesis that the suppression of pyruvate dehydrogenase activity by amino acid supplementation reduced muscle endurance. Although a high protein diet is a well-known stimulus for increased skeletal muscle content in healthy subjects, it may deteriorate renal function in those with mild renal insufficiency.[10] The creatinine clearance in young 5/6Nx mice fed a high protein diet did not differ compared to mice fed on low protein in this study, but the creatinine clearance may not fully reflect the renal function in mice with different amounts of muscle volume. More precise measurement of glomerular filtration rate would help clarify the relationship between renal function and muscle endurance.

To clarify the reason behind the altered mitochondria content in skeletal muscles in mice

with chronic renal insufficiency, the authors demonstrated that serum tumor necrosis factor-alpha (TNF-α) and 8-OHdG levels were increased in 5/6Nx mice and that stimulation with TNF-α and interleukin-6 as well as acrolein and 4-hydroxynonenal, which are mediators of oxidative stress, reduced PGC-1α expression and increased B-cell lymphoma 2/adenovirus E1B 19 kDa protein-interacting protein 3-like (BNIP3L) expression in C2C12 myocytes, resulting in reduced mitochondria content. The successful demonstration of reduced mitochondria content in cultured myocytes exposed to inflammatory cytokines or oxidative stressors gives valuable insight into the *in vivo* mechanism linking chronic renal insufficiency and skeletal muscle impairment. Analyzing the effect of accumulated uremic toxins on muscle volume may also be beneficial.

Previous reports analyzing the skeletal muscle mitochondria in CKD patients are conflicting. One report showed that skeletal muscle mitochondrial function was preserved in six patients on dialysis[11], whereas another report showed that patients with stage 3 or 4 CKD exhibited a reduction of mitochondria in skeletal muscle[12]. The latter report also showed that exercise training increases muscle mitochondrial content in patients with CKD[12], which might account for the diversity of mitochondria content in patients with CKD.

More detailed study of the mechanisms linking muscle volume and endurance reduction in CKD may benefit patients and provide a useful clinical strategy to maintain physical activity in CKD patients.

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LEGEND

Figure 1 **Decrease of muscle volume in renal insufficiency.** In subtotal nephrectomized mice, inflammatory cytokines and oxidative stress were elevated in the plasma, which reduced PGC-1α and phosphorylated AMPK. Young mice with renal insufficiency exhibited decreased mitochondrial content and reduced exercise endurance, but maintained muscle volume and power. In contrast, aged mice with 5/6 nephrectomy showed reduced muscle volume and power as well as decreased mitochondrial amount and muscle endurance. Subtotal nephrectomized mice fed a high protein diet exhibited a reduction of PDH activity in skeletal muscle, leading to a reduction in mitochondrial amount and exercise endurance. AMPK, AMP-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PDH, pyruvate dehydrogenase.

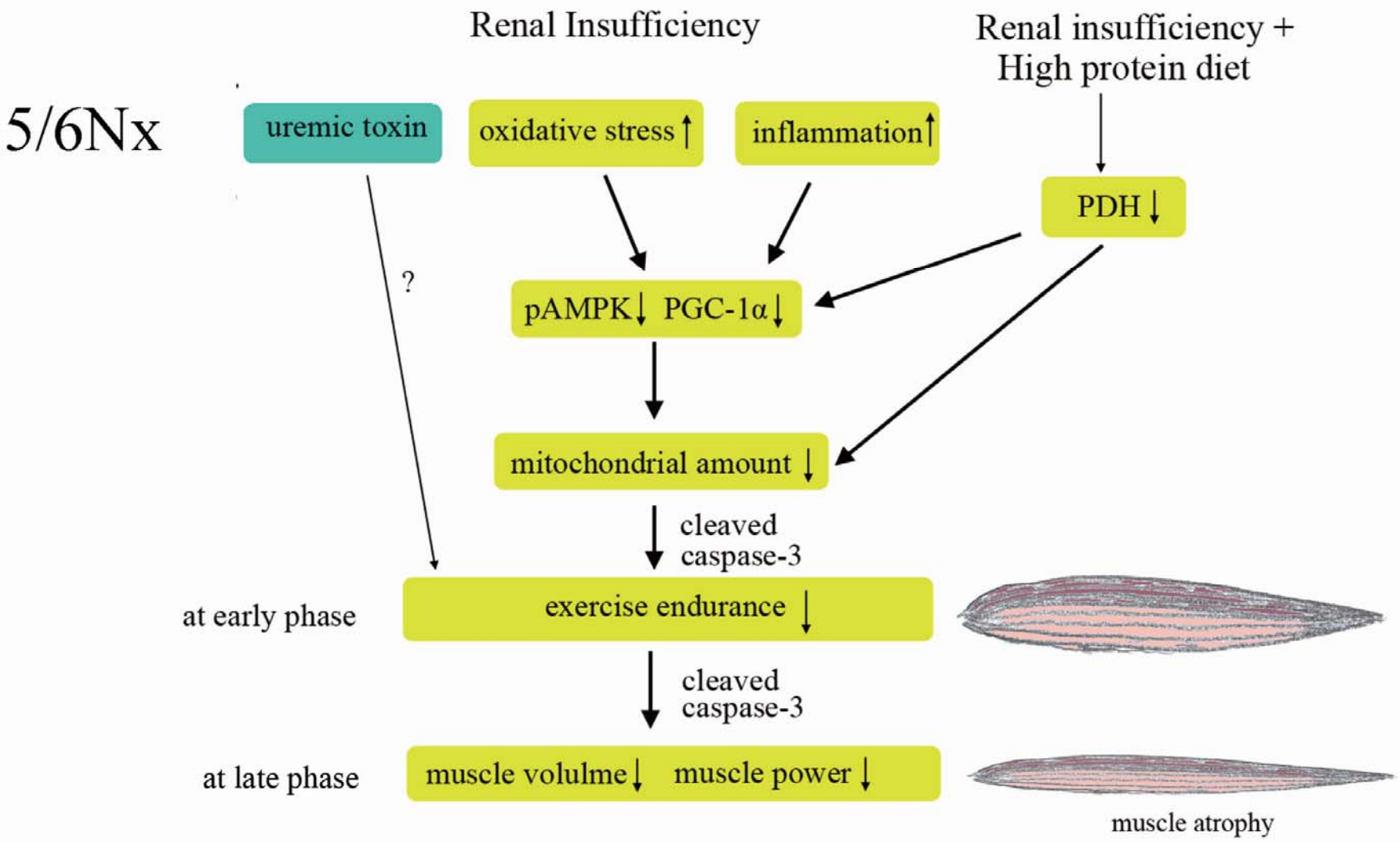

Figure 1 Yokoi, Yanagita